REMARKS

Claims 1-69 were originally presented in the present application. Claims 1-12 and 70 are currently pending. Claim 15 is cancelled herein by amendment and without prejudice to Applicants' rights to pursue this claims in other patent applications.

Amendments to the Claims

Applicant has currently amended Claims 1 and Claim 70. As noted above, Claim 15 is cancelled herein by amendment and without prejudice to Applicants' rights to pursue these claims in other patent applications.

Support for Claim Amendments

Support for each claim amendment can at least be found in the specification as originally filed as follows.

For "up to about 20%" in Claim 1, see page 16, line 16 ("a marked increase (approximately 20%) in the lifespan of mice") and the results of Figure 4.

Claim Rejections under 35 U.S.C. §112, first paragraph

Examiner rejected previously pending Claims 1, 3-12, 15 and 70 under 35 U.S.C. § 112, first paragraph, alleging that the specification, while being enabling for the lifespan of mice, does not reasonably provide enablement for extending the lifespan of mammals or mammalian cells in general using the disclosed C60 compounds.

Enablement of increased longevity in mice and humans.

The claims as currently amended are drawn to a method of extending the lifespan of a *mouse,* a *human*, or a *cell thereof*, and thus render the Examiner's arguments as to enablement of extending the lifespan of a *mammal* or a *mammalian cell* moot. The Applicants have made this

amendment simply to accelerate the prosecution of this application before the Office and reserve their right to pursue similar claims directed to mammals or mammalian cells in subsequent continuations of this patent application. However, the Examiner has also alleged that the specification has only enabled methods of increasing the lifespan of mice, and not humans.

The Examiner has found unpersuasive the Applicants' arguments that the testing done in mice (in vivo system) disclosed in the current application satisfies the enablement requirement of 35 U.S.C. §112. The Examiner states:

> "While Applicant has provided evidence in the form of animal tests (i.e., only mice), the reliance on such evidence to support the utility of the present invention in humans…is, respectfully, insufficient. Applicant has failed to establish, either in the present disclosure or the remarks submitted in response to the present rejection, that an experimental mouse model was recognized in the art as a model with predictive value in establishing efficacy of lifespan-extending therapies in humans or other mammals." (Page 6, end of paragraph 2)

Examiner's rejection relies upon *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971) which states in part:

> "[A]ssuming that sufficient reasons for doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, *such a rejection can be overcome by suitable proof indicating that teaching contained in the specification is truly enabling*." (emphasis added)

Applicant respectfully directs Examiner's attention to the following references as proof that establishes that experimental mouse models are indeed recognized in the art as a model with predictive value in establishing efficacy of lifespan extending therapies in humans.

Mice are art-accepted models for extending lifespan.

The introductory paragraph of Roth et al. (Science, 305:1423, 2004) reads:

> "As gerontological research continues to gain both visibility and interest within the broader scientific community, the relevance of various model systems for eventual application of findings to humans has become a critical issue. Although *rodents remain the most widely used animal model for gerontology*, an increasing use of invertebrates has provided many new insights into aging processes, especially regarding the possible longevity genes. Given the complexity of human physiology, however, models more phylogenetically similar to humans are needed." (emphasis added)

In considering this statement, we first note that the authors state that even more distantly related invertebrate model systems are useful in the study of aging. The relevance of invertebrate model systems such as worms and flies in studying aging is thus accepted by those skilled in the art. Second, the authors cite the need for models more phylogenetically similar to humans to justify their experiments conducted in rhesus monkeys. Those skilled in the art would agree that given the resources and technical capability to perform such experiments, non-human primate models are very relevant. The question at hand however is not what model theoretically is the most predictive, but rather what models were recognized in the art as having predictive value.

What this statement makes clear is that models such as rodents and even invertebrates are viewed by those skilled in the art as having predictive value.

Applicants believe that this reference should address the Examiner's concern that the "Interventions Testing Program" reference, did not provide any express statement or teaching that mice are art-accepted models for extending lifespan (Page 6, paragraph 3). Roth et al. (ibid) clearly and expressly states that rodent models are, and have been, the most widely accepted model for the study of aging with potential relevance to human aging and age-related disease. Although the Roth et al. article was published in 2004, it refers to the state of the art during the relevant timeframe.

Mice have been used to study potential life extending treatments in humans.

A specific example of the use of mice by skilled artisans in the study of potential life-extending treatments for humans was conducted by Pugh and colleagues (Pugh et al., 1999). DHEA is an adrenal steroid hormone that is widely consumed by people who believe it may keep them "younger longer." In their studies, Pugh and colleagues examined DHEA supplementation in mice to determine if it could increase lifespan in that model system. "DHEAS supplementation was selected because of extensive current human usage in the face of limited data to support the benefits of this practice" (Pugh et al., 1999, first paragraph of Discussion, second sentence). Pugh et al. ultimately determined that DHEAS supplementation had no significant effect on the lifespan of mice, consistent with their observation that there is limited data supporting any effect in humans. In contrast, Pugh et al. found that positive control mice subjected to caloric restriction did exhibit lifespan increases relative to non-calorically restricted controls. The fact that the authors undertook and published this study is entirely consistent with

the Applicants' position that those of skill in the art do in fact regard rodent systems as having predictive value with respect to humans.

Evidence of correlation/Lack of evidence that the model does not correlate.

The Examiner states (beginning at the bottom of Page 7 and continuing onto Page 8):

> "Applicant has failed to make an objective showing of evidence or sound scientific reasoning that would reasonably correlate the efficacy shown in mice to be an adequate projection of the same or substantially similar efficacy in humans… In the present case, a person having ordinary skill in the art would have been highly skeptical to extrapolate the results shown in mice to…humans, particularly in the absence of any scientific basis for such an extrapolation."

The Examiner cites language from both *Ex parte Balzarini*, 21 USPQ2d 1892 (B.P.A.I. 1991), "There is no evidence of record that experimental animal models have been developed in this area which would be predicative of human efficacy," and *Ex parte Maas*, 9 USPQ2d 1746 (B.P.A.I. 1987), "It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans…"

The Applicant will set forth sound scientific basis for such extrapolation below by demonstrating the correlation between mouse and human models of aging, thus "establish[ing] the significance of the [in vivo] experiments set forth in their specification." *Maas*, 9 U.S.P.Q.2d at 1748.

First, Applicants address the cited case law. The present application is distinguishable from *Ex parte Maas* for several reasons. In *Maas*, the Examiner analyzed a "defect in

experimental design" of the in vivo studies described (the Board did not provide details of this defect). *Mass,* 9 U.S.P.Q.2d at 1748. In the present case however, the Examiner has not identified any defects in experimental design that would question the truthfulness of Applicants' assertions. Secondly, there was a letter of record in *Maas* that led to the Board's conclusion that "animals have not yet been bred for which appellant's 'vaccine' is useful and the in vivo studies performed thus far have been inconclusive." *Maas*, 9 USPQ2d at 1748. Again, the Examiner in the present case does not identify evidence that the Applicants' invention is not useful or that the in vivo studies performed by Applicants have been inconclusive.

The present case is also distinguishable from *Ex parte Balzarini*. In *Balzarini*, the Examiner supported her assertion that those skilled in the art would question the objective truth of the Applicants' application with references directly relevant to the subject matter (anti HIV treatments). One reference the Board found especially persuasive was a scientific review article claiming that at the relevant time, those skilled in the art did not associate successful in vitro treatment of HIV infected human cells with any probability of achieving success in in vivo treatment of the disease. *Balzarini*, 21 U.S.P.Q.2d at 1895. In the current application, Examiner cites the "Animal Diversity Web" (Page 8), an online database of animal natural history, distribution, classification and conservation biology. Examiner posits that this reference supports a notion that the diversity between mice and man would lead one skilled in the art to be highly skeptical of Applicants' assertions. Great diversity between species may naturally lead those unskilled in the art to general skepticism of a correlation between the effects of a given treatment on different organisms. However, those skilled in the art recognize that diversity amongst

organisms does not necessarily preclude correlation. In fact, diverse species share many conserved mechanisms, especially with respect to fundamental biological processes.

A prime example of how conservation can occur across diverse species is the life extending properties of caloric restriction. Calorie restriction (CR) has been shown to increase lifespan in studies of vastly diverse species (mice, rats, hamsters, dogs, fish, spiders, Nematodes, Drosophilia, and yeast) (Weindruch, 1998; Masoro, 2000). Especially relevant to the current application is the fact that reductions in oxidative stress have been shown to result in lifespan increases in non-mammalian, non-vertebrate organisms such as C. elegans (Melov et al., 2000) and Drosophila (Sohal and Weindruch, 1996), and as disclosed by Applicants, antioxidant treatment can extend the lifespan of mice. Invertebrates such as worms and flies are more distantly related to vertebrates such as mice than mice are to other vertebrates such as humans. Thus, one skilled in the art would not be skeptical in believing that the life expanding properties of antioxidants observed in mice would extend to humans.

Examiner cites studies of deprenyl treatment as evidence of lack of uniformity between mouse and human results in longevity studies (bottom of Page 12, continuing onto Page 13; Specification, bottom of Page 3, continuing onto Page 4). Examiner points out that various deprenyl studies in humans have had conflicting results, and thus cast doubt upon the usefulness of a mouse model as suggestive of human activity. However, the Applicants respectfully point out that results in the deprenyl studies were inconsistent in rodent models to begin with. In fact, the cited study done in C57B6 mice (the same mouse strain used in Applicants' C60 experiments) failed to show any survival benefits from deprenyl treatment (Specification, Page 4, lines 11-13). Therefore, conflicting or negative results observed in human studies were

consistent with, not contrary to, results observed in rodent models for deprenyl treatment. In addition, unlike antioxidants, the age extending mechanisms of deprenyl have not been correlated to the same age extending mechanisms as caloric restriction (Deprenyl is a selective monoamine oxidase (MAO) B inhibitor (Specification Page 3, lines 20-21)). Thus, evidence from deprenyl studies should not be given the same weight as Applicants' antioxidant results. Further, Section 2164.02 of the MPEP states, "Even with such evidence, the Examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

Examiner, in the first paragraph of Page 11 states, "While it is acknowledged that Turturro et al. speculates that the biomarkers identified in rodents would be readily extrapolated to humans, Turturro et al. expressly states that such is an ***assumption*** and is not fact" (emphasis in original). To refute this point, the Applicants respectfully direct the Examiner's attention to specific examples of correlation of biomarkers between rodents and humans.

First, it is well established that during human aging, plasma IGF-1 levels decline (Sonntag et al., 1992; Breese et al., 1991). It has also been established that "age-related decreases in IGF-1 [occur] in all mammals tested to date and appear to be an important correlate of the aging process" (Breese et al., 1991, first paragraph of Discussion). Because of this correlation, Sonntag and colleagues tested caloric restriction in mice (see also Breese et al., 1991 for rat studies) to determine its effects on plasma levels of IGF-1. The clear rationale for this experiment is that the effect of caloric restriction in mice on the decline of IGF-1 during aging would be predictive of the effect of caloric restriction's effect on declining IGF-1 during human aging.

Another example of the correlation between lifespan-expanding treatments in mice and humans was reported in Fontana et al., 2004. Caloric restriction studies in rats and mice show a marked decrease in cellular proliferation and inflammation. Similarly, Fontana et al. found that in a study of humans voluntarily living on a calorie restricted diet, caloric restriction reduced inflammation and the risk of developing atherosclerosis.

The most significant results highlighting the correlation between mouse models of lifespan extension and human physiology come from the Biosphere 2 experiment (Walford et al., 1999; 1992). The so-called "Biospherians" were locked in the Biosphere and were subjected to a low calorie, but nutrient dense diet very similar to the calorie restricted diet recognized as the most robust and reproducible non-genetic means of slowing aging in animals. Physical examination of these subjects revealed that:

> [B]lood glucose, insulin, and glycated hemoglobin were all significantly decreased in the crew members inside Biosphere 2. The same changes have been found in rodents and monkeys, except that in monkeys glycated hemoglobin did not decrease. Leucopenia in response to CR occurs in both rodents and monkeys, and was also found in humans living in Biosphere 2. In the Biosphere 2 crew members, thyroid-related hormones T3, T4, rT3, and TSH responded similarly to CR in humans as in rodents. (Walford et al., 1999, Page 64, column 2, paragraph 4)

There remains speculation that, "some of the physiological and psychological effects of caloric restriction that occur in animals may impact the human life very differently (Dirks and Leewenburgh, 2006). However, such is speculation and the authors report that, "Signs of CR

efficacy that occur in animals, such as reduced blood glucose, insulin, body temperature, and blood pressure, also occur in humans." The Applicants respectfully point out that the case law does not require a rigorous or an invariable exact correlation:

> [Based] upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonably based upon the probative evidence. *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985).

As a whole, the above correlations provide sound scientific evidence to one skilled in the art, and lend strong support to the supposition, that mouse models are reasonably predictive of human activity in lifespan extending treatments.

The Examiner has also objected to Applicants' assertion that studies showing that reductions in oxidative stress can result in lifespan increases in mice, as well as non-mammalian organisms, can be the basis for one skilled in the art to conclude that proper antioxidant treatment may extend human lifespan. Detached from the rest of the art without further evidence, Examiner's point is well taken. However, the oxidative stress model of human aging is widely recognized by those skilled in the art. (see Masoro, 2000; Beckman and Ames, 1998; Sohal and Weindruch, 1996; Yu, 1996; Sohal et al, 1994). Further, the correlation between the lifespan extending mechanisms of caloric restriction and reduction of oxidative stress is also widely recognized in the art:

> "The current perception holds that the antioxidative action of [CR] seems far more widespread than earlier suspected… Many hypotheses, which were based

> on epiphenomenal observations, could not be substantiated by the anti-aging action of [CR] and were, therefore, discounted. The oxidative stress theory is an outstanding exception that has endured [CR] scrutiny… Based on these findings, we have proposed that the ability to attenuate oxidative damage may be the major underlying mechanism of the anti aging effect of [CR]" (Yu, 1996; see also Masoro, 2005; Masoro, 2000; Sohal and Weindruch, 1996; Sohal et al., 1994).

These statements thus directly address the Examiner's previous concern that "The disparate nature of the treatment used in Turturro et al. (i.e., natural dietary modifications) versus the treatment used in the present claims (i.e., C60 fullerenes) does not lend itself to be suggestive or predictive of the activity of C60 compounds…" (sentence spanning Page 11 and 12 of the previous response). Although these treatments are different, they are not "disparate" as they apparently involve a common mechanism (i.e., an anti-oxidant effect). Given the robust, life extending nature of caloric restriction and the wide recognition in the art that reductions in oxidative damage are in part responsible for the anti-aging effects of caloric restriction, Applicants' assertion that proper antioxidant treatment may extend human lifespan would not be a surprising result to one skilled in the art.

As disclosed in Example 4 of the current application (Pages 22-26), compositions of C60 contain antioxidant properties. Specifically, the ability of C60 to catalytically eliminate superoxide radicals and hydrogen peroxide was demonstrated by a variety of assays.

Applicant respectfully directs the Examiner's attention to MPEP § 2164.02 which states:

> [I]f the art is such that a particular model is recognized as correlating to a specific condition, *then it should be accepted as correlating unless the Examiner has*

evidence that the model does not correlate. In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (emphasis added).

In this instance, the Applicants have demonstrated that the particular model (i.e., caloric restriction and the related effects of anti-oxidants) is recognized by the art as correlating to a specific condition (i.e., increases in lifespan).

Extrapolation of life span.

The Examiner states that "the current claims recite extension of up to 32%, but a direct ration of lifespan results in astounding values." (Page 9). The Examiner also points out that this value was based on the greatly extended survival of one mouse, and that it is not statistically demonstrative of the lifespan extension that would be expected in all mice or humans. Claim 1 has currently been amended to take into account Examiner's comments and to recite an extension of up to 20% beyond the generic expected lifespan, which as pointed out by the Examiner, is supported in the specification on Page 16, line 16, and in the results of Figure 4. Given an extension of up to 20%, and the Examiner's figure of average human lifespan as approximately 80 years, this would result in an extension of human lifespan by approximately 16 years. This would therefore result in a human lifespan of approximately 100 years.

As astutely recognized by the Examiner, the longest lived control mouse described in the specification lived 32 months. The longest lived treated mouse was reported as 33 months old. Thus, C60 treatment does not necessarily extend maximum lifespan, but the specification clearly supports an increase over the average lifespan. Skilled artisans may be of the belief that there exists an upper limit to human lifespan (Dirks and Leeuwenburgh, 2006). However, although achieving centenarian status is rare, it is regularly achieved. The currently amended claims recite

an increase over the generic expected lifespan, but not an increase in humans over the maximum lifespan. In order to realize how reasonable it is to suggest an extension of 16 years beyond the average human life expectancy by slowing the ravages of oxidative damage, one need only consider the near doubling of average lifespan from around 45 years to approximately 80 years that occurred during the 20th century due to advances in nutrition, healthcare, and hygiene. Thus, Applicants respectfully submit that an extension of up to 16 years beyond the average life expectancy is not so unusual an outcome that it would not be reasonably expected by those involved in the study of aging.

Scope of enablement.

The Examiner also raises the point concerning the breadth of a claim relevant to enablement (Page 5, first full paragraph). Examiner states, "The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation". Applicant has provided pharmacokinetic studies of C60 in mice, and toxicity studies in mice and rats (Page 15, lines 21-22 of specification). The Federal Circuit has held in *Cross* and *Brana* that the enablement requirement of 35 U.S.C. §112 for claims directed to asserted therapeutic uses is satisfied in cases where compounds were only tested in vivo or model in vivo systems (i.e., mice):

> Usefulness in patent laws, and in particular in the context of pharmaceutical inventions, *necessarily includes the expectation of further research and development*. The stage at which an invention in this field becomes useful is well

> before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. In view of all the foregoing, we conclude that Applicants' disclosure complies with the requirements of U.S.C. §112 ¶ 1. *In re Brana*, 51 F.3d 1560.

Fine tuning dosages for human application based on pharmacological results obtained in animal studies is routine in the art. Thus, Applicants have provided in their application sufficient teaching so that those in the art can make and use the entire scope of the invention without "undue experimentation."

Experimental Controls.

Examiner further raises the question of whether difference in feeding (in particular whether mice were subject to caloric restriction) or genetics (presence of longevity genes) may be attributable to observed differences in lifespan (Page 16 first full paragraph; Page 17 first full paragraph).

With respect to the effect of feeding, it is art accepted practice in studies of aging to state whether animals or humans have been subjected to caloric restriction when reporting such data. Applicants did not report any caloric restrictions as none were imposed. Nonetheless, Applicants establish for the record that both the treated and untreated mice of the experiment reported in Figure 4 of this application were fed ad libitum. Consequently, the longevity effect observed can be attributed to the C60 fullerene administration rather than to some combination of dietary and

compound-mediated effects as postulated by the examiner. Given that the treated mice did not exhibit any decrease in weight relative to the control mice (Specification Page 22, line 2-3), there is no reason to believe that the treated mice were somehow preferentially subjected to any caloric restrictions that could have accounted for the observed effects on longevity.

All of the mice used in Applicants' longevity studies were of the same inbred genetic strain (C57B6NIH; Specification Page 21, lines 1-2). The use of inbred strains is standard in the art to ensure genetic uniformity. Although this is not expressly stated in the specification, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Moreover, the specification further reveals that the inbred strain of mice were obtained from the National Institute of Agings mouse colonies, so it is very difficult to imagine a scenario where the treated population was somehow comprised of mutant mice as the Examiner posits. In fact, the presence of any dwarf mice in the treated population would have been obvious and presumably been reflected in a reductions in weight of the treated mice. As noted above, no such treatment-specific reductions in weight were observed.

The Applicant respectfully submits that one skilled in the art has ample scientific basis for believing that the instant invention, which disclosed the administration of an effective catalytic antioxidant that results in increased lifespan in mice, has enabled treatments for increasing the lifespan of humans.

CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants respectfully request that the Examiner reconsider and withdraw each rejection. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that a personal communication will expedite prosecution of this application, she is invited to telephone the undersigned agent at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

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